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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,507	04/20/2005	Jonathan Alexander Terrett	2543-1-039PCT/US	2619

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,507	TERRETT, JONATHAN ALEXANDER	
	Examiner	Art Unit	
	Sean E. Aeder	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-10 and12-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 4/4/07 in response to the Office Action of 1/4/07 are acknowledged and have been entered.

Claims 1-22 are pending.

Claims 1-10 and12-20 have been withdrawn.

Claims 11 has been amended by Applicant.

Claims 11 and 21-22 are currently under examination.

The following Office Action contains NEW GROUNDS of rejections necessitated by New Considerations.

Rejections Withdrawn

The rejection of claims 11, 21, and 22 under 35 U.S.C. 102(b) is withdrawn in view of amendments.

New Rejections bad on New Considerations

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 21, and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are drawn to a method of inhibiting colon tumor cell growth comprising administering any antibody to a polypeptide consisting of SEQ ID NO:1.

The specification discloses that the mRNA encoding SEQ ID NO:1 is overexpressed in colon cancer tissues as compared to normal colon tissue (Figure 4, in particular). The specification also prophetically describes a method for treatment of colon cancer comprising administering an antibody that specifically binds to one or more polypeptides which comprise or consist of the amino acid sequence of SEQ ID NO:1 or a variant or fragment thereof (pages 19-20, in particular). Further, a Declaration by Alasdair Stamps states that increased immunohistochemical staining was demonstrated

in human colon cancer tissue specimens incubated with a RAIG1 antibody as compared to the staining of adjacent tissues with a "negative control antibody". It is noted that it is unclear what is meant by the "negative control antibody" of the Declaration. Therefore, it is unclear whether expression of RAIG1 is elevated in colon tumor cells as compared to cells of normal colon tissue.

The specification lacks working examples demonstrating that any antibody of the claimed method would treat colon cancer with any predictability of success. As set forth below, this invention is highly unpredictable.

Those of skill in the art recognize the unpredictability of treating tumors with antibodies. For example, Jain (Scientific American July 1994), discloses barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all (page 60 column 3, in particular); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61 column 1 paragraph 1, in particular); (4) Convection is a necessary mechanism by which larger therapeutic molecules such as antibodies reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 column 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61 column 1through page 63

column 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63 column 2). Further, in the late 80's, Dillman (Annals of Internal Medicine, Volume 111, pages 592-603, 1989) summarized (see abstract) the status of in-vivo use of monoclonal antibodies for treating cancer wherein despite advances in biotechnology, many major hurdles persist including tumor cell heterogeneity and lack of cytotoxicity. More recently, Weiner (Seminars Oncology, Vol. 26, No. 4, 1999, pages 41-50) provided an overview of monoclonal antibody therapy including some promising activity, however major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets, and insufficient target specificity (page 43).

Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, 1997, 278:1041-1042.) who discusses the potential shortcoming of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with cologenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041 first column, in particular) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Further, those of ordinary skill in the art recognize that treatment in vivo is not predictive. The instant situation is analogous to that of *In re* Brana (34 U.S.P.Q. 2d 1436, 1440 (Fed. Cir. 1995)). A review of *In re Brana* reveals an application that claimed a chemical compound for treating a cancer, wherein the chemical compound was structurally similar to known compounds that have known in vivo use to treat tumors, and more importantly, Applicant provided in vivo data that the claimed compound could treat tumors in mice, hence it was ruled that the claimed compound was enabled for treating tumors. In the instant application, the claims are not drawn to a method of treatment using an antibody which has known in vivo ability to give rise to a therapeutic effect. Further, the instant specification provides no in vivo data, particularly demonstrating that the antibody of the claimed method would predictably give rise to a therapeutic effect in vivo. In view of *In re Brana*, Examiner asserts that successful use of in vivo mouse models of colon cancer enables methods using particular compositions for specific therapeutic effects in humans and does not require human clinical testing; however, the instant application is claiming a method of treating colon cancer using an antibody without providing any in vivo data, hence the claimed invention is not enabled. All of this underscores the criticality of providing workable examples which are not disclosed in the specification, particularly in an unpredictable art, such as antibody-mediated therapy.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of

skill in the art to determine with any predictability, that the method would function as claimed.

In the Response of 10/6/06, Applicant argues that the Declaration by Alasdair Stamps states that one of ordinary skill in the art would expect that an antibody specific for RAIG1 would target and bind RAIG1 present on cancerous cells because RAIG1 expression is increased in cancerous cells. Applicant further indicates that while it may require some experimentation to make one or more antibodies for a RAIG1 consisting of SEQ ID NO:1, such experimentation would not be undue. Applicant further indicates that the specification provides guidance to make said antibodies, prepare pharmaceutical compositions, and determining correct dosage and routes of administration. In regards to the teachings of Jain et al, Applicant submits that Jain et al does not specifically relate to colon cancer but rather refers to large solid tumors in a generalized manner. Applicant further states that it is standard medical practice to treat large solid tumors, particularly colon cancer, with surgery followed by a therapy to destroy remaining cancer cells. Applicant further states that the teachings of Dillman do not represent the state of the art as of the filing date. Applicant further submits a copy of Adair (2005, Drug Design Reviews-Online, 3(3):209-217) and states that as of 2005, there were 18 approved monoclonal antibody products with many more in various stages of being approved. Application further states that Weiner et al relates to tumors in general and not to colon cancer. Applicant further states that Weiner et al recognizes that a tumor-specific target is require, which Applicant indicates would include RAIG1. In regards to Gura, Applicant states Gura relates only to drugs in general as a

chemotherapeutic agent but does not mention antibody therapy at all. Applicant submits that antibodies are immunotherapeutic agents, a category that is distinct from chemotherapeutic agents. Applicant further argues that chemotherapeutic agents target rapidly dividing cells and as such are not restricted to cancer cells and therefore do not specifically target cancer. Applicant further states that the last paragraph of Gura indicates that the definition of molecular targets for cancer is the preferred way forward for cancer research.

The arguments in the Response of 10/6/06 have been carefully considered, but are not deemed persuasive. In regards to the argument that the Declaration by Alasdair Stamps states that one of ordinary skill in the art would expect that an antibody specific for RAIG1 would target and bind RAIG1 present on cancerous cells because RAIG1 expression is increased in cancerous cells, polypeptide expression of RAIG1 in normal and cancerous tissues is unclear. In regards to the expression of RAIG1 polypeptide in colon cancer tissue and normal colon tissue, the specification and the art do not disclose or teach levels of RAIG1 polypeptide expression in normal colon and colon cancer tissue. In regards to the Declaration by Alasdair Stamps, it is unclear what is meant by the "negative control antibody". Therefore, it is unclear whether the declaration used the same antibody when comparing RAIG1 polypeptide expression in colon cancer tissue and normal tissue. Further, it is noted that the prior art of Cheng et al (JBC, 1998, 273(52):35008-35015) examined the expression levels of RAIG1 *mRNA* in various normal human tissues. Cheng et al teaches expression levels of RAIG1 mRNA are similar in normal colon, normal ovary, normal prostate, normal kidney tissues

and RAIG1 mRNA levels are *extremely* high in normal lung tissues. In the absence of RAIG1 protein expression data, one of skill in the art would not predict that RAIG1 protein is elevated at a such a high level in cancerous colon tissue, as compared to other normal tissues, that RAIG1 protein would predictably function as a reliable target for treatment of colon tumor cells. For example, it is noted that antibodies conjugated to a therapeutic moiety that targets normal colon, normal ovary, normal prostate, normal kidney, or normal lung tissue would not predictably inhibit colon tumor cell growth.

Examiner agrees that the state of the art is such that experimentation to make one or more antibodies for a RAIG1 consisting of SEQ ID NO:1 is not undue; however, one of skill in the art would not predict that said antibodies would treat colon tumor cell growth with any success. The prophetic guidance disclosed in the specification does not make-up for the lack of predictability of inhibiting colon tumor cell growth by administering an antibody specific for RAIG1 polypeptide.

In regards to the argument that Jain et al does not specifically relate to colon cancer but rather refers to large solid tumors in a generalized manner, Examiner agrees that Jain et al teach general pitfalls regarding antibody-based therapies that are applicable to all antibody-based therapies for solid tumors (including colon cancers tumors). Further, in regards to the argument that it is standard medical practice to treat large solid tumors, particularly colon cancer, with surgery followed by a therapy to destroy remaining cancer cells, Applicant is arguing a limitation that is not recited in the claims. The pending claims are drawn to treating *tumor* cell growth and not to treating

single colon cancer cells remaining after surgery. Treating cells of a colon *tumor* with antibodies for RAIG1 would have the pitfalls discussed by Jain et al.

In regards to the argument that the teachings of Dillman do not represent the state of the art as of the filing date, the problems regarding tumor cell heterogeneity and lack of cytotoxicity remain problems facing antibody-based therapeutics.

In regards to the argument that Adair (2005, Drug Design Reviews-Online, 3(3):209-217) states that as of 2005, there were 18 approved monoclonal antibody products with many more in various stages of being approved, Examiner agrees that the teaching of Adair are aimed at highlighting the advances in the field of antibody-based therapeutics. It is also noted that none of the antibodies discussed by Adair use RAIG1 as a target. Examiner also notes that the Adair teaching was submitted by UCB Celltech, a publicly traded biotechnology company that would have a great interest in highlighting advances in biotechnology. It is further noted that Aidair cites the teachings of Adams et al (Cancer Research, 6/01, 61:4750-4755), which teaches how the affinity of a particular antibody can hinder the ability of said antibody to function as a cancer therapeutic (see abstract, in particular). Adams et al teaches that an antibody with low affinity for its target lacks specificity, while an antibody with high affinity for its target impedes the ability of the antibody to penetrate a solid tumor (page 4753, in particular). Further, it is noted that Adams et al discusses the teachings of Jain et al that are discussed above (see left column of page 4750 and paragraph spanning pages 4752-4753, in particular), which are clearly still challenges one faces in developing antibody based therapeutics.

In regards to the argument that Weiner et al relates to tumors in general and not to colon cancer, Examiner aggress that the teachings of Weiner et al relate to all tumors (including colon cancer tumors). Further, in regard to the statement that RAIG1 is a tumor-specific target, without providing extensive profile of normal and corresponding cancer tissues, it is unclear whether RAIG1 is a tumor-specific marker. For the reasons discussed above regarding the lack of clarity in the Declaration of Alasdair Stamps, it not clear whether RAIG1 protein levels differ in normal and colon tumor cells. Further, without experimentation, one of skill in the art would be unable to predict that colon tumor cells have higher RAIG1 protein expression than the level of RAIG1 protein found in other normal tissues of a subject (see the discussion above regarding Cheng et al).

In regards to the argument that Gura relates only to drugs in general as a chemotherapeutic agent but does not mention antibody therapy at all, Gura relates to the unpredictability of cancer therapeutics in general. Further, in regards to the argument that RAIG1 is a molecular target for cancer and that chemotherapeutic agents target rapidly dividing cells and as such are not restricted to cancer cells and therefore do not specifically target cancer, without experimentation, one of skill in the art would be unable to predict that colon tumor cells have higher RAIG1 protein expression than the level of RAIG1 protein found in other normal tissues of a subject (see the discussion above regarding Cheng et al). Therefore, one of skill in the art would not predict that therapeutics targeting RAIG1 protein would target colon tumor cells over any other tissue in a subject expressing RAIG1.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA
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